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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/808,832	03/15/2001	Robert A. Copeland	PH-7134	5618

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EXAMINER	
RUSSEL, JEFFREY E	

ART UNIT	PAPER NUMBER
1654	10

DATE MAILED: 12/04/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/808,832	COPELAND ET AL.	
	Examiner	Art Unit	
	Jeffrey E. Russel	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 September 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-39* is/are pending in the application.

4a) Of the above claim(s) *33 and 34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14,20-24,30 and 35-39* is/are rejected.

7)☒ Claim(s) *15-19,25-29,31 and 32* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *9* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

1. Applicant's election with traverse of the E^{cp} group and of SEQ ID NO:186 in Paper No. 8 is acknowledged.

a) The traversal with respect to the election of the E^{cp} group is on the ground(s) that the election is inconsistent with the practice set forth in MPEP 803.02, first paragraph. This is not found persuasive because MPEP 803.02, first paragraph, concerns the situation where the members of the Markush group are sufficiently few in number and so closely related that examination of the entire claim can be made without serious burden. This situation is not present in the instant application, where literally millions of different compounds are embraced by the claims, and as shown by the prior art rejections set forth below, references which anticipate or suggest certain species do not anticipate or suggest other species. MPEP 803.02, first paragraph, is not a complete summary of Office Markush practice. In particular, MPEP 803.02, third and fifth paragraphs, support maintenance of the restriction requirement when the elected species is found to be anticipated or obvious, or when prior art is found which anticipates the Markush-type claims with respect to non-elected species. This situation is present in the instant application.

With respect to claims 15-29, the elected E^{cp} group has been examined and has been found to be novel and unobvious over the prior art of record. Accordingly, the search has been extended throughout the full scope of claims 15-29.

b) Claims 33 and 34 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected amino acid sequence. Applicant timely traversed the restriction (election) requirement in Paper No. 8.

The traversal with respect to the election of SEQ ID NO:186 is on the ground(s) that according to MPEP 2434, Applicants are entitled to have up to 10 independent and distinct

nucleotide sequences in a single application examined without restriction. This is not found persuasive because this section of the MPEP concerns the examination of nucleotide sequences, whereas the instant application involves the examination of amino acid sequences. Group policy is that only a single amino acid sequence will be searched in each application. In order to expedite prosecution of this application, it is recommended that Applicants delete the non-elected amino acid sequences from instant claims 30-32.

The requirement is still deemed proper and is therefore made FINAL.

2. The disclosure is objected to because of the following informalities: SEQ ID NOS must be inserted after every amino acid sequence subject to the sequence disclosure rules. See 37 CFR 1.821(d). Such sequences are present, e.g., at pages 2, 31, 32, 34-37, and 44, and throughout the Examples of the specification. Because of the number of paragraphs in the specification which will have to be amended in order to comply with this rule, Applicants are required to submit the corrections in the form of a substitute specification, including a marked-up copy, in accordance with 37 CFR 1.121(b)(3). The Sequence Listing filed June 28, 2001 lists 210 sequences. However, the examiner has not found any sequences in the specification or claims with a SEQ ID NO higher than 202. It is not clear where in the disclosure of the invention are located the amino acid sequences identified as SEQ ID NOS:203-210. Appropriate correction is required.

3. Claims 4-14, 20-24, and 30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 4 is indefinite because when R is the group recited at page 80, line 16, it is not clear what is attached to the second carbonyl group present in the

substituent. For analogous reasons, claim 5, page 82, line 28; and claim 30, page 95, line 1; are also indefinite. At claim 4, page 81, line 4; claim 5, page 83, line 15; and claim 30, page 95, line 18; the word "or" should be inserted after the semicolon so that standard Markush terminology is used. At claim 5, page 81, line 28; claim 10, page 84, line 22; and claim 20, page 90, line 14; the word "and" should be inserted after the semicolon so that standard Markush terminology is used. At claim 5, page 82, line 7, "and" should be inserted after the comma so that standard Markush terminology is used. At claim 10, page 85, lines 13 and 32, "or" should be changed to "and" so that standard Markush terminology is used.

4. Claims 1-19, 31, and 35-39 are objected to because of the following informalities: At claim 1, page 78, lines 2-3; claim 4, page 79, lines 25-26; and claim 5, page 82, lines 5-6; Applicants are requested to review whether "α-Ala" should instead be "β-Ala", because "α-Ala" would ordinarily be presumed from the previously recited "Ala". At claim 1, page 78, line 3; claim 4, page 79, line 26; claim 5, page 82, line 6; and claim 10, page 85, line 26; the amino acid "Cba" is repeated. At claim 10, page 86, line 16; claim 15, page 88, line 31; and claim 31, page 97, line 10; a comma or semicolon should be inserted at the end of the line. At claim 36, line 1, "administering" is misspelled. Appropriate correction is required.

5. Instant claims 1-32 and 35-39 are deemed not to be entitled under 35 U.S.C. 119(e) to the benefit of the filing date of provisional application 60/189,387 because the provisional application, under the test of 35 U.S.C. 112, first paragraph, does not disclose, e.g., all of the E^{cp} groups recited in the instant claims. Accordingly, Trouet et al (U.S. Patent No. 5,962,216) is available as prior art against the instant claims under 35 U.S.C. 102(b).

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for the purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

For the purposes of this invention, the level of ordinary skill in the art is deemed to be at least that level of skill demonstrated by the patents in the relevant art. Joy Technologies Inc. v. Quigg, 14 USPQ2d 1432 (DC DC 1990). One of ordinary skill in the art is held accountable not only for specific teachings of references, but also for inferences which those skilled in the art may reasonably be expected to draw. In re Hoeschele, 160 USPQ 809, 811 (CCPA 1969). In addition, one of ordinary skill in the art is motivated by economics to depart from the prior art to

reduce costs consistent with desired product properties. In re Clinton, 188 USPQ 365, 367 (CCPA 1976); In re Thompson, 192 USPQ 275, 277 (CCPA 1976).

7. Claims 1 and 2 are rejected under 35 U.S.C. 102(b) as being anticipated by Trouet et al (U.S. Patent No. 5,962,216). Trouet et al teach the prodrug compound Gly-Leu-Gly-Leu-DNR (see column 13, SEQ ID NO:13). The compound is hydrolyzed in the presence of MCF-7/6 (mammary carcinoma cells) conditioned medium to release daunorubicin. This compound corresponds to Applicants' claimed compound in which E^{cp} is Cap-Gly-Xp1-Xp2-Laa where Cap is R which is hydrogen. Note that Applicants' claims permit Cap/R to be hydrogen because at claim 33, page 99, SEQ ID NO:8 has only hydrogen atoms at its N-terminus. Daunorubicin is a doxorubicin analogue.

8. Claims 35-39 are rejected under 35 U.S.C. 103(a) as being obvious over Trouet et al (U.S. Patent No. 5,962,216). Application of Trouet et al is the same as in the above rejection of claims 1 and 2. Trouet et al does not teach administering the prodrug compound in combination with a pharmaceutically acceptable carrier in order to treat breast cancer/carcinoma. It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to use the prodrug compound of Trouet et al to treat breast cancer/carcinoma because it is desirable to treat such a disease and because Trouet et al teaches that daunorubicin, a useful therapeutic agent, is released from its prodrug form by enzymes present in breast cancer/carcinoma cells. It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to administer the prodrug of Trouet et al in combination with a pharmaceutically acceptable carrier because it is routine in the art to administer therapeutic agents in combination with pharmaceutically acceptable carriers for ease of storage, transportation, measurement, and administration. It would have been obvious to one of ordinary

skill in the art at the time Applicants' invention was made to administer the prodrug compound of Trouet et al to breast cancer/carcinoma cells by non-intravenous methods, e.g., by direct injection, because Trouet et al disclose that the enzymes present in blood will also hydrolyze the prodrug compound and it would be desirable to avoid premature release of the daunorubicin from the prodrug.

9. Claims 1-14 are rejected under 35 U.S.C. 103(a) as being obvious over Trouet et al (U.s. Patent No. 5,962,216) as applied against claims 1 and 2 above, and further in view of the WO Patent Application 00/64486. More generally, Trouet et al teach a terminal group Z, especially succinyl, linked through a peptide Z to a therapeutic agent M, especially doxorubicin. The peptide Z is cleaved by enzymes secreted by the target cells so as to permit entry of the therapeutic agent into the target cells. See, e.g., the Abstract; column 3, lines 11-37; column 4, lines 8-12; and claims 1, 3-6, and 12. Trouet et al do not teach a peptide Z which is cleavable by a matrix metalloproteinase and which corresponds to Applicants' elected E^{cp} group. The WO Patent Application '486 teaches an amino acid sequence Pro-Leu-Gly-Leu-Trp-Ala which is cleaved by matrix metalloproteinases. The amino acid sequence can be used to form drug conjugates which are cleaved by the enzyme. Matrix metalloproteinases are associated with tumors and are necessary for metastasis. See, e.g., page 37, line 20 - page 38, line 6. The amino acid sequence of the WO Patent Application '486 corresponds to Applicants' elected E^{cp} group as defined in instant claims 1, 4, 5, and 10. It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to form the prodrugs of Trouet et al using the amino acid sequence taught by the WO Patent Application '486, because Trouet et al's prodrugs can be formed using any peptide which is cleaved by an enzyme, and because the WO Patent

Application '486's amino acid is sequence is described as being cleavable by an enzyme which is associated with the tumor cells which are to be treated by Trouet et al.

10. Claims 1-5 and 35-39 are rejected under 35 U.S.C. 102(b) as being anticipated by Monsigny et al (U.S. Patent No. 4,703,107). Monsigny et al teach the anti-tumoral prodrugs PHA-Gly-Gly-L-Arg-L-Leu-Daunorubicin and PHA-Gly-Gly-L-Arg-L-Leu-Adriamycin (i.e. doxorubicin). The drugs are liberated from the prodrugs in the vicinity of tumoral cells by proteases excreted from the tumoral cells. The prodrugs can be combined with pharmaceutically acceptable carriers. See, e.g., column 1, line 61 - column 2, line 2; column 4, lines 18-24, 44, and 46; and column 6, line 67 - column 7, line 22. The prodrugs correspond to Applicants' claimed compound in which E^{cp} is Cap-Xa2-Gly-Xp1-Laa or Cap-Gly-Xp1-Xp2-Laa where Cap is R which is a polyhydroxyalkanoyl.

11. Claims 1-14 and 35-39 are rejected under 35 U.S.C. 102(e) as being anticipated by Firestone et al (US 2002/0147138 A1). Firestone et al teach the enzyme-activated anti-tumor and anti-metastatic prodrug N-Cbz-Gly-Phe-Ala-Leu-doxorubicin. The peptide portion of the prodrug is capable of being cleaved by collagenase(IV) or elastase. The prodrugs are used to treat cancer, e.g., breast carcinoma. See, e.g., paragraphs 18, 27, 28, and 42 and claims 8-10. This prodrug corresponds to Applicants' claimed compound in which E^{cp} is Cap-Gly-Xp1-Xp2-Laa. With respect to instant claims 6-9 and 11-14, in view of the similarity in structure between the peptide portion of the prodrug of Firestone et al and Applicants' claimed E^{cp} groups, the former are deemed inherently to be cleavable by the matrixins specified in these claims. Sufficient evidence of similarity is deemed to be present between the prodrug of Firestone et al

and Applicants' claimed compounds to shift the burden to Applicants to provide evidence that the claimed compounds are unobviously different than that of Firestone et al.

12. Claims 15-19 would be allowable if rewritten to overcome the claim objections set forth in this Office action and to include all of the limitations of the base claim and any intervening claims. Claims 20-24 would be allowable if rewritten or amended to overcome the rejection(s) under 35 U.S.C. 112, second paragraph, set forth in this Office action. Claims 25-29 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. The prior art of record does not teach or suggest E^{cp} groups having the particular combinations of R groups and amino acid sequences required by these claims.

Claim 30, limited to elected SEQ ID NO, would be allowable if rewritten to overcome the rejection(s) under 35 U.S.C. 112, second paragraph, set forth in this Office action and to include all of the limitations of the base claim and any intervening claims. Claim 31, limited to the elected SEQ ID NO, would be allowable if rewritten to overcome the claim objections set forth in this Office action and to include all of the limitations of the base claim and any intervening claims. Claim 32, limited to the elected SEQ ID NO, is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. The prior art of record does not teach or suggest an E^{cp} group having the structure, in particular the gamma-glutamic acid residue and the O-benzyl-serine residue, of the elected SEQ ID NO.

Monsigny et al (U.S. Patent No. 4,703,107) is not applied against instant claims 6-9 because there is no disclosure in Monsigny et al that their peptides are cleaved by the particular

matrix metalloproteinases specified in these claims, and because there is insufficient structural similarity between the prodrugs of Monsigny et al and Applicants' disclosed compounds in order to support a finding of inherency.

The Timar et al article (Cancer Chemother. Pharmacol., Vol. 41, pages 292-298) has been carefully considered but is not deemed by itself to teach or suggest the instant claimed invention. In particular, the residues Pro-Gln-Gly-Ile of the Timar et al article's melphalan hexapeptide do not correspond to or suggest any of Applicants' E^{cp} groups. The Timar et al article does not teach or suggest inserting melphalan into any other position within the peptide Pro-Gln-Gly-Ile-Ala-Gly which represents the collagenase-cleavable site in collagens.

13. The reference crossed off of the Information Disclosure Statement filed November 18, 2002 is a duplicate citation.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey E. Russel at telephone number (703) 308-3975. The examiner can normally be reached on Monday-Thursday from 8:30 A.M. to 6:00 P.M. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Brenda Brumback can be reached at (703) 306-3220. The fax number for Art Unit 1654 for formal communications is (703) 305-3014; for informal communications such as proposed amendments, the fax number (703) 746-5175 can be used. The telephone number for the Technology Center 1 receptionist is (703) 308-0196.

Jeffrey E. Russel
Primary Patent Examiner
Art Unit 1654

JRussel
December 3, 2002